

### **REMARKS**

Claims 1, 7-9, 14-29, 31-34, 36, 45, 46, 86-90, 212, 213, 263-267 and 280-296 were pending in the application. Claim 29 is canceled without prejudice. Claims 1, 284, 285, and 293-296 have been amended for clarity of language. No new matter has been added by the amendments. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

### **CLAIM OBJECTIONS**

The Examiner objected to claims 293, 294, 295, and 296 for the recitation of “an exon.” In response, Applicants have amended claims 293, 294, 295, and 296 in accordance with the Examiner’s suggestion, to replace “an exon” with “said exon.” Thus, the objections of claims 293, 294, 295, and 296 should be withdrawn.

### **THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN**

The Examiner rejected claim 29 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Without making any admissions as to the merits of the Examiner’s rejection, and in order to expedite prosecution of the instant application, Applicants have canceled claim 29. As such, the rejection of claim 29 under 35 § U.S.C. 112, first paragraph, is obviated.

### **THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN**

The Examiner rejected claims 1, 7-9, 14-29, 31-34, 36, 45, 86, 87, 89, 90, 263-265, and 280-296 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In particular, in paragraph 7 on page 4 of the Office Action, the Examiner alleges that Claim 1 is vague and indefinite because step (b) of claim 1 does not require measuring levels of hybridization between probes that specifically hybridize to different variants of an exon of a gene, but rather only requires measuring levels of hybridization between said probes and said RNAs or nucleic acids, and as such, said levels of hybridization cannot indicate the nucleic acid expression levels of said plurality of different variants. The Examiner also

alleges that Claim 1 is vague and indefinite because “said probes in step (b) do not only limit to probes that specifically hybridize to different variants of an exon of a gene” (see the Office Action at page 4, paragraph 7). In response, Applicants have amended step (b) of claim 1 to recite “measuring levels of hybridization between said plurality of polynucleotide probes and said RNAs or said nucleic acids,” thereby clarifying that hybridization levels are measured for the plurality of polynucleotide probes. Applicants respectfully point out that the antecedent basis for “said plurality of polynucleotide probes” in step (b) of claim 1 is found in step (a) of claim 1, which recites that the plurality of polynucleotide probes “comprises” a probe that specifically hybridizes to one of said different variants of an exon of a gene, for each gene in the plurality of different genes. Since the term “comprises,” when used in a claim, means the same as “includes but is not limited to,” it is clear that the plurality of polynucleotide probes recited in step (a) includes at least one probe (for each gene in the plurality) that specifically hybridizes to one of said different variants of an exon of a gene, and can also include one or more probes that do not specifically hybridize to one of said different variants of an exon of a gene. The plurality of probes in step (b) need not be limited to probes that specifically hybridize to one of said different variants of an exon of a gene. Nevertheless, by virtue of including in the plurality of probes the probes that specifically hybridize to an exon variant, the levels of hybridization indicate the expression levels of exon variants for genes in the plurality of genes.

In paragraph 8 on page 4 of the Office Action, the Examiner further contends that claim 1 is vague and indefinite because step (b) of claim 1 does not require that said nucleic acids are RNAs, and as such it is unclear why said levels of hybridization in step (b) of claim 1 can indicate the nucleic acid expression of said plurality of said different variants. Applicants respectfully point out that the antecedent basis for “said nucleic acids” in step (b) of claim 1 is found in step (a) of claim 1, which recites a “nucleic acid sample comprising RNAs or nucleic acids derived therefrom.” Thus, the “nucleic acids” referred to in step (b) are nucleic acids that are derived from RNA, *e.g.*, cDNAs that are reverse transcribed from RNAs, or cRNAs derived from cDNAs (see the specification at page 45, line 14 to page 46, line 26). Accordingly, the levels of hybridization between said plurality of probes and said nucleic acids in step (b) are indicative of nucleic acid expression of said plurality of variants, and the Examiner’s rejection is obviated.

The Examiner further contends that claim 1 is vague and indefinite because step (a) of claim 1 “only requires one probe that specifically hybridizes to one of said different variants of an exon of a gene, [and thus] it is unclear why the expression levels of said exon variants

of a plurality of different genes in the genome of an organism in a cell sample derived from said organism can be analyzed” (see the Office Action, at page 4, paragraph 8). In response, Applicants point out that claim 1 recites that the plurality of polynucleotide probes “comprises a probe that specifically hybridizes to one of said different variants of an exon of a gene, for each gene in said plurality of different genes.” Thus, the claim requires use of at least one probe specific to an exon variant, for each gene in the plurality of genes, resulting in a minimum of a plurality of exon variant-specific probes, one for each gene. Since each exon variant specific probe “specifically hybridizes” to a particular exon variant of a gene, thereby distinguishing the expression of that exon variant from other exon variants, expression levels of exon variants of different genes are thereby analyzed.

In paragraph 9 on page 4 of the Office Action, the Examiner further contends that claim 265 is vague and indefinite because “it is unclear that said perturbation is exposed what to a drug” (see the Office Action at page 4, paragraph 9). Applicants admit to some confusion as to the alleged basis for the Examiner’s rejection. Nonetheless, Applicants submit that claim 265 is clear and definite. Claim 265 depends from claim 86, which recites “[t]he method of claim 1, wherein said cell sample has been subjected to a perturbation.” Claim 265 recites “wherein said perturbation is exposure to a drug.” As such, claim 265 should be read as “[t]he method of claim 1, wherein said cell sample has been subjected to a perturbation, wherein said perturbation is exposure to a drug.” Thus, it is clear from the language of claims 1, 86, and 265 that claim 265 requires that the cell sample of claim 1 has been exposed to a drug. Support for claim 265 can be found in the specification at *e.g.*, page 16, lines 31 to 33, which teaches that responses of a cell sample to a perturbation, such as the application of a drug, can be measured by observing the changes in the biological state, *e.g.*, the exon expression state or the transcriptional state of the cell sample.

In paragraph 10 on page 4 of the Office Action, the Examiner contends that claim 284 is vague and indefinite because step (b) of claim 284 does not require measuring levels of hybridization between exon specific probes and/or variant junction probes and said RNAs or nucleic acids, but rather only requires measuring levels of hybridization between said probes and said RNAs or nucleic acids, and as such, said levels of hybridization cannot indicate the nucleic acid expression levels of said plurality of different variants. In response, Applicants have amended step (b) of claim 284 for clarification purposes, to recite “measuring levels of hybridization (i) between each of said exon specific probes and said RNAs or said nucleic acids, and (ii) between each of said variant junction probes and said RNAs or said nucleic acids.” The rejection is thus obviated.

In paragraph 11 on page 5 of the Office Action, the Examiner further contends that claim 284 is vague and indefinite because step (b) of claim 1 does not require that said nucleic acids are RNAs, and as such, it is unclear why said levels of hybridization in step (b) of claim 284 can indicate the nucleic acid expression of said plurality of said different variants. As discussed above for claim 1, the antecedent basis for “said nucleic acids” in step (b) of claim 284 is found in step (a) of claim 284, which recites a “nucleic acid sample comprising RNAs or nucleic acids derived therefrom.” Thus, the “nucleic acids” referred to in step (b) are nucleic acids that are derived from RNA, *e.g.*, cDNAs that are reverse transcribed from RNAs, or cRNAs derived from cDNAs (see the specification at page 45, line 14 to page 46, line 26). Accordingly, the levels of hybridization in step (b) are indicative of nucleic acid expression of said plurality of different variants, and the Examiner’s rejection is obviated.

In paragraph 12 on page 5 of the Office Action, the Examiner alleges that claim 285 is vague and indefinite because step (b) of claim 1 does not require measuring levels of hybridization between variant junction probes and said RNA or nucleic acids, but rather only requires measuring levels of hybridization between said probes and said RNAs or nucleic acids, and as such, said levels of hybridization can not indicate the nucleic acid expression levels of said plurality of different variants. The Examiner also alleges that Claim 285 is vague and indefinite because “said probes in step (b) do not only limit to variant junction probes” (see the Office Action, at page 5, paragraph 12). In response, Applicants have amended step (b) of claim 285 for clarification purposes, to recite “measuring levels of hybridization between said plurality of junction probes and said RNAs or said nucleic acids,” thereby clarifying that hybridization levels are measured for the plurality of junction probes. Applicants respectfully point out that the antecedent basis for “said plurality of junction probes” in step (b) of claim 285 is found in step (a) of claim 285, which recites that the plurality of junction specific probes “comprises” a variant junction probe for each of a plurality of different variants of at least one exon for each gene in said plurality of different genes. Since term “comprises,” when used in a claim, means the same as “includes but is not limited to,” it is clear that that the plurality of junction specific probes recited in step (a) includes at least one variant junction probe (for each of a plurality of different variants of at least one exon for each gene in said plurality of different genes), and can also include one or more junction specific probes that are not variant junction probes. The plurality of junction specific probes in step (b) need not be limited to variant junction probes. Nevertheless, by virtue of including in the plurality of junction specific probes a variant junction probe for

each of a plurality of different variants of at least one exon for each gene in said plurality of different genes, the levels of hybridization indicate the expression levels of exon variants for genes in the plurality of genes.

In paragraph 13 on page 5 of the Office Action, the Examiner alleges that:

claim 285 is rejected as vague and indefinite in view of the second “wherein” phrase of step (a). Since the first part of the second “wherein” phrase only requires one variant junction probe while the second part of the second “wherein,” phrase requires two or more variant junction probes (i.e., each of said variant junction probe), the first and second parts of the second “wherein” phrase do not correspond each other.

Applicants submit that the “wherein” clause of step (a) of claim 285 to which the Examiner is referring, recites “wherein said plurality of junction specific probes comprises a variant junction probe for each of a plurality of different variants of at least one exon for each gene in said plurality of different genes, each of said variant junction probes being a probe specific to a junction region of said variant and an adjacent exon in a multiexon comprising said variant of said exon, each of said different variants being a different splice form of said exon generated using a different 3' or 5' splice junction of said exon, and each of said variant junction probes being a probe specific to a junction region of said variant and an adjacent exon in a multiexon comprising said variant of said exon” (emphasis added). Since the first part of the “wherein” clause specifies a variant junction probe for each of a plurality of different variants of at least one exon for each gene in said plurality of different genes, the first part of the foregoing “wherein” clause requires a plurality of variant junction probes, which thus can properly be referred to in the plural form in the second part of the foregoing “wherein” clause. The rejection is thus obviated.

In paragraph 14 on page 5 of the Office Action, the Examiner further contends that claim 285 is vague and indefinite because step (b) of claim 1 does not require that said nucleic acids are RNAs, and as such, it is unclear why said levels of hybridization in step (b) of claim 285 can indicate the nucleic acid expression of said plurality of said different variants. As discussed above for claims 1 and 284, the antecedent basis for “said nucleic acids” in step (b) of claim 285 is found in step (a) of claim 285, which recites a “nucleic acid sample comprising RNAs or nucleic acids derived therefrom.” Thus, the “nucleic acids” referred to in step (b) are nucleic acids that are derived from RNA, e.g., cDNAs that are reverse transcribed from RNAs, or cRNAs derived from cDNAs (see the specification at page 45, line 14 to page 46, line 26). Accordingly, the levels of hybridization between said

plurality of probes and said nucleic acids in step (b) are indicative of nucleic acid expression of said plurality of variants, and the Examiner's rejection is obviated.


In view of the foregoing remarks and claim amendments, Applicants respectfully request that the rejections of claims 1, 7-9, 14-29, 31-34, 36, 45, 86, 87, 89, 90, 263-265, and 280-296 under 35 U.S.C. § 112, second paragraph, be withdrawn.

### **CONCLUSION**

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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